Bioequivalence Recommendations for Vancomycin HCL Capsules - Generic Industry Positions

GPhA-Sponsored Presentation

FDA Advisory Committee Meeting

August 4, 2009

Presentation Outline

- Scientific Perspective
  - Russell J. Rackley, Mylan Pharmaceuticals
- Clinical Pharmacy Perspective
  - Doug Slain, West Virginia University Hospitals
- Medical Perspective
  - Dale Coy, Advocate Healthcare System
- Final Conclusions

Scientific Perspective

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Generic Industry Positions

- Vancocin® HCl Capsules were approved on the basis of cross-over study of oral solution vs Vancocin® Capsules in normal healthy subjects
  - clinically relevant concentrations of fecal vancomycin were found to be comparable, with respect to efficacy
  - plasma and urine concentrations were negligible, suggesting no absorption, with respect to safety
  - it is inferred that solubilization of the formulation must be a key requirement of any oral vancomycin formulation
  - These considerations hold true for generic oral formulations today.

Generic Industry Positions

- There are no known tangible Safety or Efficacy considerations that would distinguish administration of oral solution versus oral capsule product.
  - This was basis of approval for capsule product.
  - This is also current sentiment of practicing clinicians.

Generic Industry Positions

- Current draft guidance recommendations for demonstrating bioequivalence are excessive
  - Current draft guidance recommendations for test product formulations allow for in vitro or in vivo options for demonstrating bioequivalence
  - Recommendation of strict Q1 and Q2 requirement (Qualitatively & Quantitatively similar) relative to Reference-Listed-Drug **and** recommendation of an in vivo study with clinical endpoints in patients with Clostridium Difficile Associated Diarrhea (CDAD) is not grounded in a fundamental understanding of oral vancomycin therapy. These should not be technically required.

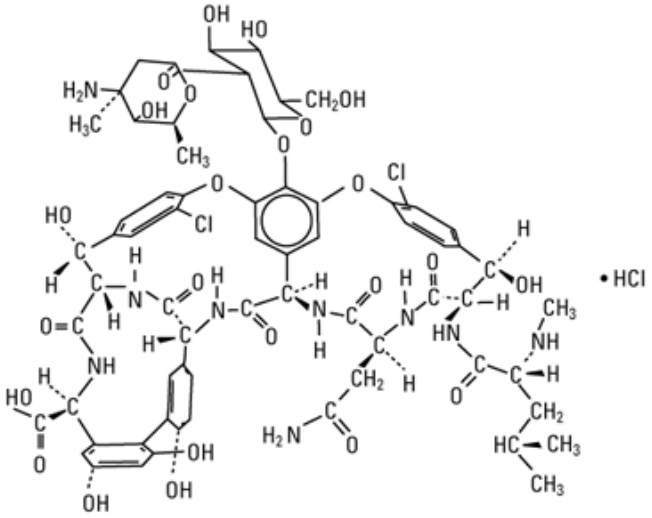
Generic Industry Positions

- Recommendation of a clinical study is counter to the agency's longstanding guiding principle that no unnecessary human research should be done.

- Demonstration of equivalency may be based on careful evaluation of relevant dissolution behavior, similar to or faster than Vancocin® capsules.

Scientific Rationale to Consider Solubilization

- Vancomycin HCl, Mol. Wt. 1486



- Considered to be highly soluble over physiologic pHs.
- Degree of solubility will more than accommodate the maximum dose at one time (i.e. ~500mg within 250mL).

Scientific Rationale

FDA Vancomycin Solubility Evaluation

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Vancomycin HCl	pH 1 mg/mL	pH 3 mg/mL	pH 4 mg/mL	pH 5 mg/mL	pH 7.5 mg/mL
Sample 1	140	192	2.97	9.73	17.7
Sample 2	141	192	3.02	9.35	17.6
Sample 3	140	192	2.96	9.42	17.4
Sample Mean	140	192	2.98	9.5	17.5

Scientific Rationale to Consider Solubilization, Brand Reference

- Believed to be formulated in a capsule to facilitate taste masking.
- Rate of dissolution of the Reference product, according to standard USP methods, demonstrate effective solubility to be considered satisfactory to treat Staphylococcus aureus-induced enterocolitis or Clostridium difficile infection, infections of the GI tract.

Scientific Rationale - Dissolution

- USP Method I (Rotating Basket)
  - 900 mL purified water, 100 rpm, 37° C
  - NDA specs Q75% in 45 minutes
  - USP specs Q85% in 45 minutes
- ANDA Method (Rotating Basket)

  Proposed by FDA (robust challenge)
  - 900 mL, pH 1.2, 4.5 & 6.8, 100 rpm, 37° C

Scientific Rationale

FDA Capsule Dissolution Evaluation of Vancocin®

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Dissolution Study	Lot Number	Capsule Dose (mg)	Vancomycin Percentage Release (%) (average, n = 6 capsules)					
			5min	10min	20 min	30 min	45 min	60 min
BCS pH 1.2	431233	250	4.6	23.1	62.4	89.1	101.7	100.9
BCS pH 1.2	431737	250	4.6	25.2	67.0	89.3	94.2	93.1
BCS pH 1.2	A200240	250	6.9	26.9	68.2	91.0	94.7	95.9
BCS pH 4.5	431233	250	1.1	7.2	36.1	71.4	101.3	105.3
BCS pH 4.5	431737	250	0.8	6.1	31.6	59.3	85.8	98.7
BCS pH 4.5	A200240	250	2.2	11.4	41.5	74.5	95.2	96.5
BCS pH 4.5	429915	125	0.5	9.9	44.2	84.9	95.8	96.5
BCS pH 6.8	431233	250	0.8	8.7	33.4	63.3	93.2	96.9
BCS pH 6.8	431737	250	1.2	8.1	36.3	70.4	83.3	N/A
BCS pH 6.8	A200240	250	2.3	11.8	42.8	76.9	98.3	99.6
USP SGF pH 1.2	431233	250	4.5	24.2	68.5	90.2	99.0	99.5
USP SIF pH 6.8	431233	250	4.2	10.7	31.9	50.1	74.9	86.9

Scientific Rationale – Dissolution

- Formulation is not really complex, rather a type of immediate-release oral formulation.
- The dissolution process may be considered important from a QA perspective

Scientific Rationale – Conclusions on Dissolution

- Dissolution is rapid enough for Vancocin® capsules to be considered equivalent to administration of an oral solution
  - basis of approval for Vancocin® caps, and the indications and D&A are the same as for solution, and used interchangeably
- Adequate time for dissolution allowed, for transit from mouth to site of infection, within the GI. Drug is largely in solution by the time drug enters the duodenum. Approved for SAE & CDI patients.

Scientific Rationale – Relevance of IV solution use

- Current IV labeling allows for preparation for oral administration, including addition of flavoring. This has been a long-standing practice and is probably led to the approval of Vancocin® Solution (now off market).
- Current IV powder formulations "… may be diluted in 1 oz. of water and given to the patient to drink. The diluted material may be administered via nasogastric tube. Common flavoring syrups may be added to the solution to improve the taste for oral administration."

Scientific Rationale – Relevance of IV solution use

- There has been no apparent concern regarding addition of excipients to vancomycin IV solution for oral administration nor concern over interaction, this diminishes any real concern of a requirement of Q1/Q2 or clinical endpoint study.
- By its very use, Vancocin® Capsules may be considered as a standard solid oral formulation, interchangeable with oral vancomycin solution and hence effectively functioning similar to a solution.

Scientific Rationale – Relevance of IV solution use

- One must conclude that solubilization of an oral vancomycin formulation is the key requirement to achieving therapy. This can be readily demonstrated in vitro.
  - Many solid oral dosage forms are approved on basis of in vitro dissolution testing . . . AA-rated products, BCS1 biowaiver products.

Scientific Rationale - Biopharmaceutic Inference

- Vancomycin is recognized as being highly soluble [though non-penetrating through membranes, staying within GI tract].
- As we know, oral administration of oral vancomycin was originally approved based on administration of solution.
- The capsule formulation has not undergone clinical safety and efficacy testing, though it is considered to have an equivalent therapeutic effect relative to oral solution.

Vancocin® Capsule Approval

Excerpts from the FDA Medical Officer's Review of Antibiotic Form *[NDA]* 50-606 (July 10, 1985)

1. The applicant *[The Lilly Research Laboratories]* already markets vancomycin powder for oral solution in one-gram and ten-gram screw-cap containers.
2. It is approved for the treatment of staphlococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by Clostridium difficile.
3. Proposed indications *[for the capsule product]* are identical to those which are already approved for the marketed oral vancomycin *[for oral solution].*
4. No specific clinical efficacy data are filed *[in NDA 50-606 for the capsules].*
5. The applicant wishes to refer to clinical data filed in the Antibiotic Form *[NDA]* 61-668 for oral vancomycin *[Vancocin® for Oral Solution]*.
6. A bioavailability study was conducted. The aim of the study was to compare the absorption and overall bioavailability of vancomycin in an oral solution with that in an oil-paste capsule formulation.

Vancocin® Capsule Approval

Excerpts from the FDA Medical Officer's Review of Antibiotic Form *[NDA]* 50-606 (July 10, 1985)

Vancomycin oral solution was compared to a capsule formulation in 12 healthy adult subjects:

Six subjects received single doses of 6 mL reconstituted oral solution or two 250 mg capsules according to a randomized crossover design. Mean recovery of vancomycin in urine did not exceed 0.1% of the dose. Blood vancomycin levels were undetectable (sensitivity 0.5mg/L).

Six volunteers received either 3 mL of reconstituted oral solution or 250 mg capsules of vancomycin every eight hours for seven doses in a randomized crossover design. No blood levels were detected (sensitivity 0.6 mg/L) and urinary recovery did not exceed 0.76% over the treatment periods.

No difference concluded between the two formulations, based on comparable high fecal concentrations and a lack of blood and urine concentration.

Basis for approval of oral capsule

- The oral capsule was approved based on bridging studies, which primarily investigated similarity of fecal concentrations in cross-over evaluations of oral capsule vs. oral solution. In essence, approval was based on recognition of a lack formulation effect of the capsule relative to the solution, indicating that solubilization of vancomycin from the oral capsule was not considered to be limiting to clinical efficacy [or decreased safety].
- Failure to accept this premise would draw the original approval of the capsule product into question.
- **No controlled studies are known to have been sponsored by ViroPharma, or included in a study, other than use as a comparator. No clinical endpoint design studies are known to have ever been conducted primarily for Vancocin® Capsules!**

Transition of Vancocin® to ViroPharma - Historical Context of Oral Capsules

- IV approved in 1967, with provision for oral administration
- Vancocin® Oral Solution introduced later
- Vancocin® Capsules introduced without specific clinical efficacy data.
- There was overlap in time when oral Vancocin® solution and capsules were available.
- Oral solution and capsules could be used essentially interchangeably, affirming a lack of uniqueness of the oral capsule.
- Vancocin® acquired by ViroPharma in 2004.
- Vancocin® Oral Solution taken off market leaving only Vancocin® Capsules as only finished dosage form for oral administration.

ViroPharma Annual Report, 2004

Excerpts

VIROPHARMA INCORPORATED CORE VALUE DRIVERS

COMPOUND	DISEASE	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	MARKETED
Vancocin® Pulvules® HCl	*C. difficile* Colitis, *S. aureus* Enterocolitis*					
Maribavir	Cytomegalovirus					
HCV-796	Hepatitis C					
Intranasal Pleconaril	Common Cold	Under development by Schering-Plough Corporation				

*Approved indication: Antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile* and enterocolitis caused by *Staphylococcal aureus*

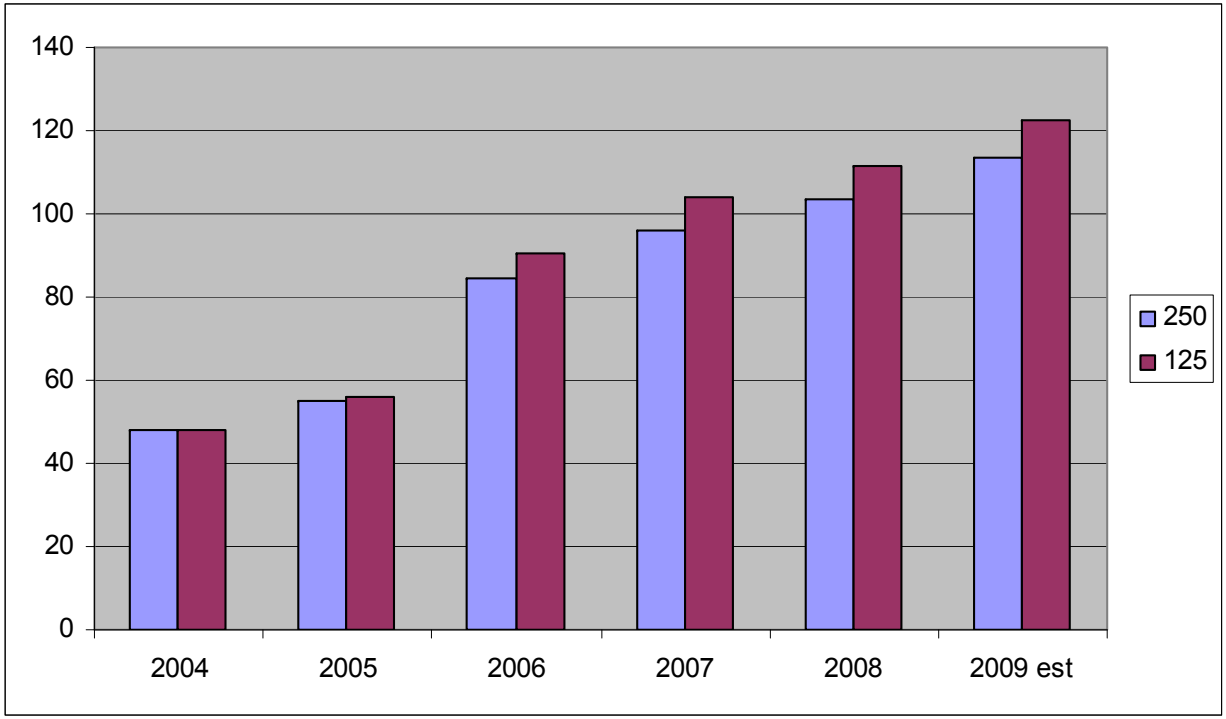
During 2004, we fulfilled a promise that we made to our shareholders several years ago: to become a pharmaceutical company that develops and commercializes drugs that improve and save the lives of patients. We did so through our purchase from Eli Lilly and Company of Vancocin® Pulvules, an important orally administered product used to treat two lower intestinal tract bacterial diseases.

Recent History of Vancocin® Capsules

- As Vancocin® capsules have been the sole source of 'finished' dosage formulation of oral vancomycin since 2004, dramatic price increases have been observed.
- "OGD's representations regarding the requirement of clinical studies to demonstrate BE to Vancocin were a key factor to ViroPharma's decision to acquire Vancocin from Lilly in late 2004."
  [Viropharma Petition, May 31, 2006]

Vancocin® Price (per gram basis)

Source: IMS Data, Annual Reports and Pricing



Price has nearly tripled since acquisition in 2004.

Price per gram basis, is approximately 20 times that of IV Vancomycin (which can be administered orally).

Price-Driven Usage of Oral Solution

- Oral Vancocin® solution was withdrawn from market around 2004, leaving only Vancocin® Capsules, as finished product for oral administration.
- Current economic demands have driven many institutions toward utilizing IV preparations compounded for oral administration. This is driven, in part by the exorbitant cost of Vancocin® capsules (20-fold higher than IV).
- Introduction of generic vancomycin HCl capsules will alleviate price constraints around Vancocin® Capsules.

Federal Register Notice

- Federal Register notice of Dec. 16, 2008, announced availability of a Draft Guidance for Industry on Bioequivalence Recommendation for Vancomycin HCl capsules, for public comment.

Draft Guidance

- Current draft guidance is based on recognition that equivalency can be based on in vitro evaluation, with respect to similar dissolution characteristics across physiological relevant conditions.
- Though similar formulation characteristics are recommended (Q1/Q2), the fundamental criteria of equivalence should be ability of the test formulation demonstrate similar dissolution characteristics as the reference.
- Alternative to in vitro characterization, an in vivo clinical end point study in patients was recommended (something the Innovator never performed for this formulation)

Rationale for Bioequivalence - Dissolution

- In vitro dissolution testing across physiologic conditions provides a high level of assurance that a proposed generic product would complete solubilization prior to reaching the site of action within the GI tract.
- In theory, FDA's recommendation that generic vancomycin capsule products have dissolution profiles matching those of Vancocin® ($f_2 \geq 50$) is overly restrictive and could be broadened to permit f_2 values below 50 if the generic product dissolves at least as fast as Vancocin®.

Rationale for Bioequivalence - Equivalence to Oral Solution

- Due to the inherent solubility characteristics, vancomycin capsule products may be thought of as essentially equaling delivery of oral solutions.
  - Oral solutions are allowed a waiver of in vivo bioequivalence, particularly if, among other things, the proposed product contains no inactive ingredient that may significantly affect systemic or local availability for products intended to act locally.

Rationale for Bioequivalence - Excipient Concerns

- Efficacy not affected - potential interaction on effectiveness of vancomycin is moot point since all formulations are tested via USP antimicrobial test
- Solubility not affected - excipient effects are guarded by extensive in vitro characterization of dissolution
- Absorption not affected - excipients effects are rare to this regard and only tend to occur in presence of very large amounts of excipients
- Vancocin® labeling does not prohibit administration with other medications, food or beverages, which may be viewed as additional 'excipients‘. This would grossly outweigh potential excipient differences with generic formulations.
- These considerations tend to negate any perceived requirement of Q1/Q2.

Therapeutic Equivalence

- The Generic Industry is in general agreement with FDA on requirements for bioequivalence, particularly as it relates to bioequivalence determination by in vitro evaluation based on dissolution testing.
- Provided a generic formulation demonstrates similar dissolution characteristics under physiologic conditions, it may be considered to be therapeutically equivalent to Vancocin® Capsules.

Clinical Pharmacy Perspective

Douglas Slain, Pharm.D., BCPS, FCCP
Associate Professor
Infectious Diseases Clinical Specialist
West Virginia University Hospitals

Current Dosing Regimen, 2009
[dailymed.nlm.nih.gov]

- Oral Capsules – for treating antibiotic-associated pseudomembranous colitis caused by C. difficile and staphylococcal enterocolitis, the usual adult total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.
- Oral solution – allowance currently made for some IV products to be prepared for oral administration, with similar dose regimen as capsules.

Increased Demand for Oral Vancomycin

- Incidence of *C. difficile* colitis appears to be increasing
- Use of oral vancomycin therapy appears to be increasing
- Metronidazole failure has been increasingly reported in the published literature
  - New hypervirulent strains now present
  - Severe disease may not respond well to metronidazole

Kelly et al. *NEJM* 2008;359:1932
CID 2005;40:1586-90., *CID* 2005;40:1591-97., *Lancet Infect Dis* 2005;5:549-57.

Increased Demand for Oral Vancomycin

- Drug susceptibility tests are not performed clinically, so treatment is empiric and based on clinical appearance and response.
- IDSA Draft *C. difficile* guidelines (presented at the 2007 Annual IDSA meeting) now lists vancomycin as first line for severe disease

IDSA= Infectious Disease Society of America

Vancocin® Capsules are Cost Prohibitive

- Cost is the major reason that oral Vancocin® capsules are NOT used
- Why does an oral drug discovered in the 1950s cost $800-1,000 for a 10 day course?
- Most hospitals use homemade oral solution, or oral use of IV vancomycin instead of Vancocin® capsules due to cost

Kucer's The Use of Antibiotics, 5th Ed.
Johnson DA. Medscape Gastroenterology, Article 702980, 2009
Stone et al. ASHP Midyear Clinical Meeting 2003,
Vancomycin Monograph, AHFS Drug Information 2009

Vancocin® Capsules are Cost Prohibitive

"*In hospitals, this issue can be avoided by administering the generic intravenous vancomycin orally, reducing the price of a 10-day course to $45. There is no reason to believe that such an approach would alter fecal levels of the drug. However, community pharmacies do not stock intravenous vancomycin and would not be interested in manipulating the product so that it could be taken orally. It is possible that generic formulations of oral vancomycin will reach the US market within the next few years*".

Jacques Pepin, M.D., M.Sc. *C.difficile* Expert

Clin Infect Dis 2008;46:1493-8.

Vancocin® Capsules are Cost Prohibitive

- Difficulty filling Vancocin® Capsule outpatient prescriptions
  - Prior approvals, drug availability, % co-pays
- 3rd party insurance will often require a first treatment with metronidazole before they will approve use of oral Vancocin® capsules. This can delay appropriate therapy.
- It is difficult to get 3rd party payers to pay for homemade oral solution, or oral use of IV vancomycin as they are not marketed oral prescription formulations.

Oral Vancomycin Is “Local” Therapy

- Labeled by the FDA as “Locally Acting”
- Oral vancomycin therapy is considered “local” therapy for *C. difficile* colitis, due to the lack of any needed systemic vancomycin exposure
- Systemically administered Vancomycin (intravenous) not shown to be effective for *C. difficile*
- Clinically , we administer the drug anyway we can: Oral capsule, homemade oral solution, or oral use of IV vancomycin. We administer these formulations orally, through NG tubes, and G-tubes. …..Even enemas.

Scientific Support for Current Oral Vancomycin Dosing

- Vancocin® Capsules approved based on small pharmacokinetic study in healthy subjects
- No well-designed trials on dose-response
- Recommended oral vancomycin dosing very broad
  - Daily dosage: 500 mg to 2 g in 3 or 4 divided doses
- Fekety et al. *Am J Med* 1989;86:15.9
  - 125mg q 6 hours (n=28) vs. 500mg q 6 hours (n=28)
  - No difference inferred [though small study], leading to 125mg recommendation [Sanford Guide, etc]

Lack of Support For Any Particular Oral Formulation of Vancomycin

- No evidence-based guideline recommends Vancocin® capsules over other forms of oral vancomycin
  - Supports that the experts condone the continued use of “homemade” oral solution or oral use of IV vancomycin

Additional points that can be made

- Not a “narrow therapeutic index” medication
- Fecal vancomycin concentrations exceed organism MIC by 10-100 times
  - *J Clin Pharm Ther* 1987;12:27-31
- *C. difficile* disease is complex and depends on factors other than specific drug concentrations in the GI tract.

A Trial With Clinical Endpoints?

- Vancocin® did not have such a trial
- A clinical endpoint study would require a very large sample size to identify a possible difference between a generic formulation and Vancocin® capsules
  - Assumption that any difference would be rare if at all.
- Prohibitive for any generic company to consider such a trial
- Such a barrier leads to the continued monopoly on marketed oral vancomycin by ViroPharma

Medical Perspective

Clostridium difficile Associated Disease (CDAD) Clinical Aspects

Dale L. Coy, MD FACG

Gastroenterology

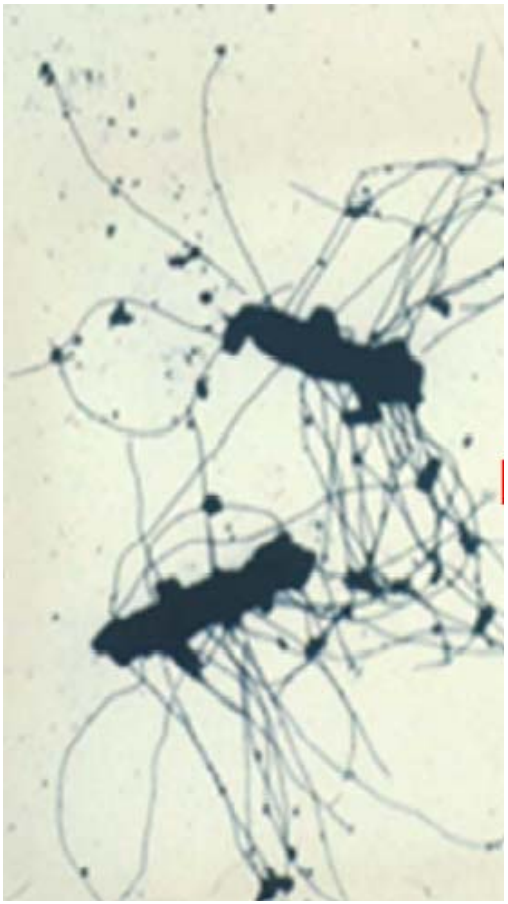
Advocate Healthcare System

Chicago, IL

Objectives

- Review *C. difficile* associated disease (CDAD)
- Describe the current epidemiology
    - Changing population at risk
    - Increasing severity
    - Increasing prevalence
- Discuss the financial impact on the US healthcare system
- Discuss antimicrobials effective for treating CDAD
- Voice the urgent need for generic oral vancomycin

Clostridium *Difficile*

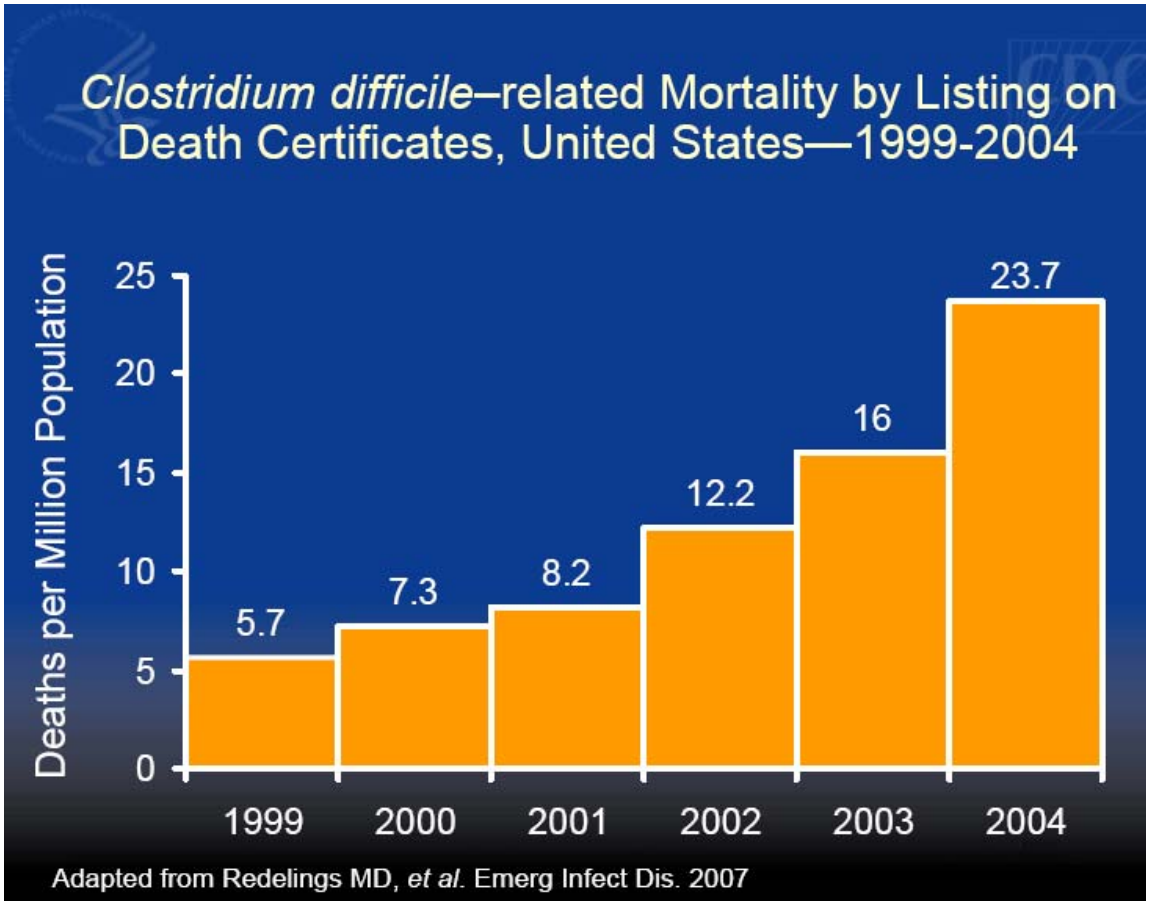


- Ubiquitous flagellated spore forming bacillus
- Spores spread by healthcare workers (hands, lab coats, stethoscopes) or hospital equipment (thermometers, toilets, x-ray machines)
- Spores live for up to 70 days
- Alcohol sanitizers are not effective in killing spores
- Difficult to prevent despite strict contact precautions

"The New Hospital Plague"

- C. *difficile* is the most common nosocomial diarrhea in adults
- Up to 35% of hospital patients colonized
- Incidence of CDAD has increased more than tenfold since 1982.
- Patients are no longer exclusively hospitalized older adults and nursing home residents (healthy adults, neonatal, peripartum women)
- Significant associated morbidity (toxic megacolon, colon perforation, shock, and death)

CDAD Mortality



Financial Burden of CDAD

- CDAD patients can average 54% higher hospital costs when compared to non-infected patients
- Hospital stays can average 55% longer

Kyne L, et al. *Clin Infect Dis*. 2002;34:346-353.

C. *Difficile* Pathogenesis

- C. *difficile organisms are* colonizers of the intestinal lumen fluid
- Not entero-invasive

Pathogenesis of CDAD

Antibiotic therapy

⇩

Alteration of colonic microflora

⇩

***C. difficile* colonization**

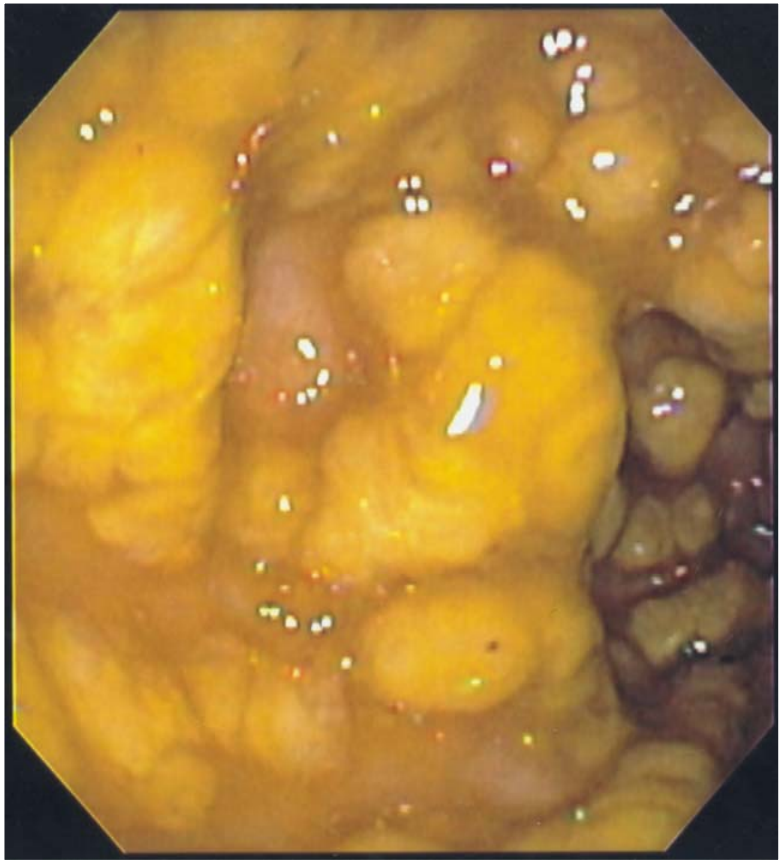
⇩

Release of toxin A, toxin B, Binary toxin

⇩

Kelly CP, et al. *Annu Rev Med*. 1998;49:375-390.

C. *Difficile* Associated Colitis



Effective Antimicrobial Therapy

- Effective therapy of CDAD depends on two major factors
  - Antimicrobial concentration in the colonic luminal fluid
  - Minimum inhibitory concentration (MIC) of the C *difficile* organism

Antimicrobial Therapy for CDAD

- Antimicrobial therapy is limited to only 2 effective antibiotics

  Metronidazole 250-500mg qid
  Vancomycin 125-250mg qid

- This offers very few choices
- Currently metronidazole is first-line – based on early studies (Cherry 1982 Teasley 1983) showing metronidazole response; 88% and vancomycin response; 90%, plus the high cost of oral vancomycin capsules, and the concern over its potential effect on the hospital environment

- "Vancomycin is more expensive than gold"
- Common practice of giving reconstituted IV powder orally

Outcomes from US Hospital Database

- Retrospective review US Hospitals 32,325 cases
- Treated Metronidazole 89%; Vancomycin 11%
- Of Vancomycin patients 48% received the IV form given orally
- Vancomycin vs. Metronidazole
  - Decreased length of stay ($p<0.0001$)
  - Decreased mortality ($p<0.02$)
  - Shorter ICU stay ($p<0.0001$)

Lahue BJ. Euro Cong Clin Micro. Abst 1732-215. 2007

Resolution of Diarrhea Vancomycin vs Metronidazole

- Time to resolution of diarrhea is shorter in patients treated with oral vancomycin

Vancomycin 3.0 days

Metronidazole 4.6 days

($p<0.01$)

Wilcox MH. J Antimicrob Chemther. 1995; 36:673-679

"Is Metronidazole Still Effective Therapy for Treating CDAD?"

- Aslam 2005; Meta-analysis of RCT's 1982-96 show no difference in efficacy between metronidazole and oral vancomycin (response rates 92-100%) while studies since 2004 show metronidazole failures have increased (16-38%) while vancomycin failures have remained the same (1-6%)
- Pepin 2005; Metronidazole treated patients that required conversion to vancomycin 1991-2002 (9.6%) 2003-2004 (25.7%)
- Zar 2007; RCT response rates 172 patients
  Mild metronidazole (90%) Vancomycin (98%)
  Severe met (76%) Vanco (97%)

Aslam S, et al. Lancet Infect Dis. 2005;5:549-557
Pepin Clin Inf Dis 2005;40:1586-1590
Zar FA. Clin Inf Dis. 2007;45:302-07

Possible Factors responsible for Changing Efficacy

- Oral Metronidazole is completely absorbed in the GI tract but fecal penetration is poor leading to low luminal concentrations (range 0.8-24 ug/g)
- susceptible range 0.2-2.0 ug/mL
- C. *difficile* isolates documented in vitro with MIC_{90} metronidazole of 32-64 ug/mL

Epidemic NAP-1 Strain

- Rapid increase in prevalence
- Hyper virulent “super bugs”
- Hyper produce tcdA, tcdB, and binary toxins (20x) leading to increased tissue injury and cell death
- Disproportionately effect older adults and may produce grave co-morbid conditions

Vancomycin

- Orally administered with limited absorption
- “Local therapy”
- Capsules are felt to be bioequivalent to liquid reconstitutes by physicians in clinical practice
- Doses oral Vancomycin 125mg vs 500mg equal
- Stool concentrations μ= 3100ug/gm (905-8760)
- C *difficile* MIC_{90} Vancomycin 0.75-2.0 ug/mL
- Resistance has not been documented (C. *difficile* isolates max MIC_{90} 4-16 ug/mL)

Kelly MD, LaMont T. NEJM. 2008;359:1932-1940
FeketyR. Am J Med 1989;86:15-19
Aslam S. Lancet. 2005;5:59557

Why is Metronidazole Still First Line Therapy for CDAD?

- Vancocin® is much higher cost
- Insurance approval limits use
- Cost is problematic when treating recurrences
  - vancomycin high dose
  - prolonged course
  - pulse treatment
  - retention enemas
- Concerns that current pricing lead to reconstitution of IV solution which might result in dosing errors and patient safety risks in the outpatient setting

Summary

- The incidence of *C. difficile* infections have increased dramatically since the current recommendations for metronidazole as first-line therapy was implemented
- Epidemic strains with new resistance patterns are of increasing importance with high morbidity and mortality
- Vancomycin will likely become first line therapy
- Access to the best antimicrobials is the logical means to protect patients at risk, keep the disease from spreading, and help reduce hospital costs

Conclusion

The availability of generic vancomycin capsules, with similar drug delivery to Vancocin® capsules, will allow a more widespread access to less expensive, more effective CDAD treatment.

Final Conclusions & Positions

Final Conclusions & Positions

- Recognizing that Vancocin® capsules were approved on a biopharmaceutics basis of comparison to oral solution, solubilization of the formulation relative to reference is recognized as a key requirement of any generic formulation.

Final Conclusions & Positions

- There are no known Safety or Efficacy considerations that would distinguish administration of oral solution versus oral capsule product.
  - This was basis of approval for capsule product.
  - This is also current sentiment of practicing clinicians.

Final Recommendation

- The Generic Industry is in general agreement with FDA on requirements for bioequivalence, as it relates to determination by in vitro evaluation based on dissolution testing, but not with respect to Q1/Q2 similarity or clinical endpoint testing.
- For all the reasons discussed, a generic formulation that demonstrates similar dissolution characteristics under physiologic conditions may be considered to be therapeutically equivalent to Vancocin® Capsules.

Questions